



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|---|--|---|
| (51) International Patent Classification ⁶ : A61K 7/16 | A1 | (11) International Publication Number: WO 99/20237 (43) International Publication Date: 29 April 1999 (29.04.99) |
| <p>(21) International Application Number: PCT/IB97/01634</p> <p>(22) International Filing Date: 17 October 1997 (17.10.97)</p> <p>(71) Applicant (for all designated States except US): ZAKRYTOE AKTSIONERNOE OBSHCHESTVO OSTIM [RU/RU]; per. Sechenovskiy, 6-3, Moscow, 119034 (RU).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only): RUDIN, Vsevolod Nikolaevich [RU/RU]; ul. Petrozavodskaya, 15-2-199, Moscow, 125502 (RU). ZUEV, Vladislav Petrovich [RU/RU]; ul. Tallinskaya, 2-316, Moscow, 123426 (RU). KOMAROV, Vladimir Fedorovich [RU/RU]; Shipilovskiy proezd, 53-5-606, Moscow, 115582 (RU). MELIKHOV, Igor Vitalievich [RU/RU]; ul. Krupskol, 19-55, Moscow, 117331 (RU). MINAEV, Vladimir Vasilievich [RU/RU]; Naberezhnaya Tarasa Shevchenko, 5-471, Moscow, 121248 (RU). ORLOV, Andrei Yurlevich [RU/RU]; ul. Kantimirovskaya, 12-1-471, Moscow, 121357 (RU). MISHIN, Anatoly Aleksandrovich [RU/RU]; ul. Obrucheva, 3-2-77, Moscow, 117421 (RU). BOZHEVOLNOV, Viktor Evgenievich [RU/RU]; ul. Bolshaya Kommunisticheskaya, 24/28-45, Moscow, 109004 (RU).</p> | <p>(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p> | |
| <p>(54) Title: STOMATIC COMPOSITION</p> <p>(57) Abstract</p> <p>This invention relates to the field of medicine, and in particular to the stomatology and may be used for preventive treatment and combatting caries, parodontitis and paradentosis. The stomatic composition on the basis of hydroxyapatite also comprises abrasive materials, humectants, thickeners, surfactants, flavouring agents, and a number of optional ingredients. The composition comprises hydroxyapatite in the form of particles of ultra finely divided hydroxyapatite with an average size by length (l), width (d) and thickness (h) of about $1 \times d \times h = 0,06 \mu\text{m} \times 0,015 \mu\text{m}; x 0,005 \mu\text{m}$ is capable to stimulate reparative osteogenesis processes and possessing a high bioactivity and specific pharmacological activity. The ultra finely divided hydroxyapatite is present in the composition in the amount of 0,1 % to 50 % by weight. The ultra finely divided hydroxyapatite is a synthetic hydroxyapatite which contains about 99,9 % of $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ by weight. The stomatic composition can be used to cure microdefects of the basic substance of the dental enamel, can be applied to prepare toothpastes, toothcreams and gels and can also be included as a component of chewing gum, pastilles, tooth elixir, formulations to rinse mouth.</p> <p><i>(different length and width) + particles surfactants and thickeners on page 4 lines 3-5, 14 to 29 to form stable suspensions and in examples, pages 1 to 8</i></p> | | |

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | | | | | | | |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania | ES | Spain | LS | Lesotho | SI | Slovenia |
| AM | Armenia | FI | Finland | LT | Lithuania | SK | Slovakia |
| AT | Austria | FR | France | LU | Luxembourg | SN | Senegal |
| AU | Australia | GA | Gabon | LV | Latvia | SZ | Swaziland |
| AZ | Azerbaijan | GB | United Kingdom | MC | Monaco | TD | Chad |
| BA | Bosnia and Herzegovina | GE | Georgia | MD | Republic of Moldova | TG | Togo |
| BB | Barbados | GH | Ghana | MG | Madagascar | TJ | Tajikistan |
| BE | Belgium | GN | Guinea | MK | The former Yugoslav Republic of Macedonia | TM | Turkmenistan |
| BF | Burkina Faso | GR | Greece | | | TR | Turkey |
| BG | Bulgaria | HU | Hungary | ML | Mali | TT | Trinidad and Tobago |
| BJ | Benin | IE | Ireland | MN | Mongolia | UA | Ukraine |
| BR | Brazil | IL | Israel | MR | Mauritania | UG | Uganda |
| BY | Belarus | IS | Iceland | MW | Malawi | US | United States of America |
| CA | Canada | IT | Italy | MX | Mexico | UZ | Uzbekistan |
| CF | Central African Republic | JP | Japan | NE | Niger | VN | Viet Nam |
| CG | Congo | KE | Kenya | NL | Netherlands | YU | Yugoslavia |
| CH | Switzerland | KG | Kyrgyzstan | NO | Norway | ZW | Zimbabwe |
| CI | Côte d'Ivoire | KP | Democratic People's Republic of Korea | NZ | New Zealand | | |
| CM | Cameroon | | | PL | Poland | | |
| CN | China | KR | Republic of Korea | PT | Portugal | | |
| CU | Cuba | KZ | Kazakstan | RO | Romania | | |
| CZ | Czech Republic | LC | Saint Lucia | RU | Russian Federation | | |
| DE | Germany | LI | Liechtenstein | SD | Sudan | | |
| DK | Denmark | LK | Sri Lanka | SE | Sweden | | |
| EE | Estonia | LR | Liberia | SG | Singapore | | |

STOMATIC COMPOSITION

DescriptionField of the Invention

This invention relates to the field of medicine, and in particular to the field of stomatology and may be used for preventive treatment and curing of caries, parodontitis and paradentosis.

Prior art

For these above-captioned purposes, stomatic compositions comprising hydroxyapatite (HA) have found an extensive application in the stomatologic practice.

There are certain compositions having a favourable effect including synthetic HA containing 92 to 97% $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, 3 to 6% H_2O and 0,3% CaCO_3 with an average particle size of 1 to 15 μm .

Such a stomatic composition, for instance, according to Patent EP 0344832 cl. A61K 7/16, comprises save the stated HA, water-soluble casein material or sodium trimetaphosphate, as an anti-caries agent and also other well known ingredients which depend upon the forms of the product manufactured, such as various humectants, binding thickeners, surfactants, flavouring agents.

The known stomatic composition (EP 03442746 cl. A61K 7/18, publ.23.11.89) supplementary includes a fluorine-containing compound in the form of NaF or sodium monofluorophosphate as an anti-caries agent.

The amount of HA present in the stomatic composition is in the range of 1 to 50%, usually 2 to 20% by weight of the stomatic composition. The stomatic composition comprises some other ingredients: humectants, thickeners, surfactants

and flavouring agents commonly known to those skilled in the art in all formulations of such products.

However, the stomatic compositions stated possess a relatively poor anti-carries effect and is not useful in the preventive medicine and in the treatment of inflammatory-destructive diseases of parodontium tissues.

Disclosure of the invention

It is an object of the present invention to create a stomatic composition comprising compounds capable to cure microdefects of the basic substance of the dental enamel to combat caries developing (e.g. to provide an anti-carries activity) and to prevent the spread of such inflammable-destructive diseases of parodontium tissues as paradenitis and parodontosis, and also compounds capable to stimulate reparative osteogenesis processes and possessing high bioactivity and specific pharmacological activity.

It is a further object of the invention to create a stomatic composition being identic to the basic substance of the dental enamel in its substance contents and crystalline parameters, as the acid formed in the materials covering dental surfaces causes destruction of mineral hydroxyapatite out of which enamel is composed and has a result due to which calcium ion loss occurs.

The task surprisingly has been solved in a composition as defined in claim 1.

A preferred composition having a more pronounced effect in view of the improvements obtained according to the invention comprises particles of hydroxyapatite with an average particle size in length (l), width (d) and thickness (h) of about $l = 0,06 \mu\text{m} \pm 50 \%$, $d = 0,015 \mu\text{m} \pm 50 \%$ and $h = 0,005 \mu\text{m} \pm 50 \%$.

A most preferred composition having a surprisingly superior effect in view of the improvements obtained according to the invention comprises particles of hydroxyapatite with an average particle size in length (l),

width(d) and thickness(h) of l about 0,06 μm , d about 0,015 μm , h about 0,005 μm .

Being introduced into the composition, HA possesses osteo-reparative properties and contains preferably about 100% $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$.

The specific surface of HA used in the composite advantageously is 100 to 150 m^2/g .

The amount of HA present in the oral composition of the present invention is in the range of 0,1% to 50%, preferably from 0,1% to 25%, and most preferably from about 0,2% to 20% by weight of the oral composition.

The composition reacts to a change in the biochemical environment, for instance a rapid dissolvment of ultra finely divided HA occurs when the pH is decreasing, that provides an active utilization of Ca and PO_4 - ions in the osteogenesis process: the size and configuration of the inventive crystals are adapted to the maximum to the dental enamel structure, which is mostly composed of HA, that suggests its use in the osteo-reparative process as a building material.

The ultra finely divided HA possesses a high adhesive-sorption activity to the dental enamel and to microdefects on its surface, that favour the preventive measures preventing the spread of caries disease and also possesses a high sorption activity in respect to proteins and aminoacids of paradenium tissues, that stimulates an active preventive treatment of the inflammable-destructive diseases such as paradenitis and paradenosis.

Moreover, the stomatic composition of the present invention will contain other conventional ingredients in addition to HA possessing osteo-reparative properties, whose introduction into the composition depends on the form of the product. For instance, in the case of an oral product in the form of dentifrice paste, cream or gel, the product will comprise a liquid phase containing humectants and binding thickeners which act to maintain the particulate solid

abrasive and HA crystals in the form of stable suspension in the liquid phase.

Surfactants and flavouring agents are also usual ingredients for various inventive embodiments of oral compositions.

The humectants usually used are glycerol or sorbitol. However, other humectants may be used according to the invention including polyethyleneglycol, propyleneglycol, lactitol and hydrogenated corn syrup. The amount of humectant will generally range from about 0% to 85% by weight of product. The remainder of the liquid phase will consist substantially of water. The liquid phase can be water or a non-aqueous composition.

As binding agents and thickeners, various substances can be used such as sodium carboxymethylcellulose, sodium hydroxyethylcellulose and xanthan gum. Natural gum bindings can be included such as gum tragacanth, gum karaya or Irish moss, etc. Any mixture of binding agents and thickeners can be also used. The amount of bindings and thickeners usually included into the oral composition is in the range of 0% to 10% by weight of the oral composition.

Moreover, any materials as widely disclosed in the literature generally also might be used for the invention as surfactants, i.e. surfactants like sodium lauryl sulphate, dodecylbenzene sulphonate and sodium lauryl sarcosinate. Other anionic surfactants also can be used as well as cationic and amphoteric and non-ionic surfactants. Surfactants are generally present in the composition in the amount of 0% to 5% by weight of the oral composition.

Flavours that are generally used in the oral compositions are those based on oils of spearmint and peppermint and might be used for the invention. Examples of other flavouring materials used are menthol, clove, wintergreen, eucalyptus and aniseed. A preferable amount of flavours is from 0% to 5% by weight in respect to the oral composition.

As abrasive materials, silica dioxide of various modifications, aluminium oxide, calcium carbonate, dicalcium phosphate anhydrite, dicalcium phosphate dihydrate, sodium metaphosphate insoluble in water, and thereof mixtures may be used. The amount of abrasive materials ranges from 0.0% to 25%. The oral composition may include a wide variety of optional ingredients. These include antimicrobial and anti-plaque agents for example chlorhexidine or 2,4,4-trichloro-2hydroxy-diphenyl ether, or zink compounds (see EPA-161898) anti-tartar ingredients such as condensed phosphates, e.g. alkali et al pyrophosphates, hexametaphosphates or polyphosphates (see US-A-4 515772 and US-A-4 627977) or zink citrates (see US-A-4 100269), sweetening agents such as saccharin. Preservatives such as formalin, sodium benzoate. colouring agents (for instance titanium dioxide) or pH-controlling agents, such as acid base or buffer agents the oral composition may also include agents enhancing the gingivitis system of the mouth cavity and representing extracts of various natural plants such as urtica, millefolium, chamomilla hypericum, salvia, etc. in the aqueous or aqueous-alcoholic forms.

The stomatic composition depending on its form (dentifrice paste, cream or gel) is maintained in contact with the tissue of the oral cavity from 15 sec to 12 hours.

The following examples of dentifrice pastes and gel comprising synthetic ultra finely divided HA possessing osteo-reparative properties as described above illustrate the invention. Percentages and parts of the components are by weight.

Belowstanding preferred embodiments of the invention are shown in its composition.

Examples N1 and 2.

Toothpaste prepared from the following ingredients.

| Ingredients, % | | |
|--|----------|----------|
| Example | 1 | 2 |
| <u>Ultra finely divided</u> | | |
| <u>Hydroxyapatite</u> | 0,2 | 2,0 |
| Silica aerogel | 22,0 | 15,0 |
| <u>Sodium carboxymethylcellulose</u> | 1,0 | 1,0 |
| Glycerol distilled | 20,0 | 20,0 |
| Sorbitol | 20,0 | 17,0 |
| Titanium dioxide | 0,6 | 0,5 |
| Sodium benzoate | 0,4 | 0,6 |
| Aqueous-alcohol extract of chamomilla | 1,0 | 0,8 |
| Aqueous-alcohol extract of hypericum | 1,0 | 0,8 |
| Sodium saccharin | 0,1 | 0,06 |
| Flavour | 1,0 | 1,3 |
| Sodium lauryl sulphate | 1,5 | 1,5 |
| <u>Water</u> | to 100,0 | to 100,0 |

Examples N 3 to 7

Toothpaste prepared from the following ingredients.

| Ingredients, % | | | | | |
|----------------------------------|------|------|------|------|------|
| Example | 3 | 4 | 5 | 6 | 7 |
| Ultra finely divided | | | | | |
| <u>hydroxyapatite</u> | 2,5 | 2,5 | 2,5 | 2,5 | 2,5 |
| Silica aerogel | 17,0 | 17,0 | 17,0 | 17,0 | 17,0 |
| Sodium | | | | | |
| <u>hydroxyethylcellulose</u> | 1,6 | - | - | 1,6 | - |
| Sodium | | | | | |
| <u>carboxymethylcellulose</u> | - | 1,1 | 1,1 | - | 0,9 |
| Sorbitol | 20,0 | 20,0 | 16,0 | 20,0 | 20,0 |
| Glycerol distilled | 20,0 | 20,0 | 20,0 | 20,0 | 20,0 |
| Polyethyleneglycol | - | - | 5,0 | - | - |
| <u>Sodium lauryl sulphate</u> | 1,5 | 1,5 | 1,5 | 1,5 | 1,5 |
| <u>Tetrasodium pyrophosphate</u> | - | 1,5 | - | - | - |
| Tetrapotassium | | | | | |
| pyrophosphate | - | - | - | 2,5 | - |
| Sodium trimetaphosphate | - | - | 2,0 | - | - |
| Zinc citrate trihydrate | - | - | - | - | 0,5 |
| Titanium dioxide | 0,6 | 0,6 | 0,6 | 0,6 | 0,6 |
| Sodium benzoate | 0,5 | 0,5 | 0,6 | - | - |
| Formalin | - | - | - | 0,05 | 0,05 |
| Aqueous-alcohol extract | | | | | |
| of salvia | 0,5 | 0,5 | - | - | - |
| Aqueous-alcohol extract | | | | | |
| of millefolium | 0,9 | 0,9 | 0,5 | 0,5 | - |
| Aqueous-alcohol extract | | | | | |
| of chamomilla | - | - | 1,0 | 0,7 | - |
| Triclosan | - | - | 0,2 | - | 0,2 |
| Sodium saccharin | 0,06 | 0,06 | 0,06 | 0,06 | 0,06 |

8

| | | | | | |
|---------|-------------------------|-----|-----|-----|-----|
| Flavour | 1,0 | 1,0 | 1,0 | 1,0 | 1,0 |
| Water | in all example to 100,0 | | | | |

Examples N8 and 9
Gel preventing paradenitis.

Ingredients, %

| Example | 8 | 9 |
|---|-----------|-----------|
| Ultra finely divided <u>hydroxyapatite</u> | 5,0 | 4,0 |
| <u>Sodium hydroxyethylcellulose</u> | 2,0 | 2,5 |
| Silica aero | 5,0 | - |
| Glycerol distilled | 10,0 | - |
| Sorbitol | 25,0 | 45,0 |
| Sodium benzoate | 0,5 | - |
| Triclosan | - | 0,3 |
| Flavour | 0,2 | 0,15 |
| <u>Sodium lauryl sulphate</u> | 0,2 | 0,15 |
| <u>Sodium saccharin</u> | 0,07 | 0,07 |
| Water | to 100,00 | to 100,00 |

Industrial application

The stomatic composition can be used to cure microdefects of the basic substance of the dental enamel, e.g. to prevent the spread of caries, and is also useful for

preventive measures avoiding the spread of inflammable-destructive diseases of parodontium tissues, such as parodontitis and parodontosis.

The stomatic composition can be used in the form of tooth pastes, tooth creams and gels. Moreover, the composition can be included as a component in chewing gum, pastilles, tooth elixir and formulations to rinse mouth.

The stomatic composition according to the invention is capable to stimulate reparative osteogenesis processes and possessing a high bioactivity and specific pharmacological activity. Moreover, this composition is useful for combatting dental caries and to prevent the spread of such inflammable-destructive diseases of parodontium tissues as parodontitis and parodontosis, on the basis of hydroxyapatite also optionally comprising abrasive materials, humectants, thickeners, surfactants, flavouring agents, and a number of optional ingredients.

Claims:

1. A stomatic composition characterised in that it comprises particles of hydroxyapatite with an average particle size in length (l), width (d) and thickness (h) of: l from about 0,2 μm to about 0,01 μm , d from about 0,1 μm to about 0.001, and h from about 0.1 μm to about 0,0001 μm .

2. The stomatic composition according to claim 1 characterised in that it comprises particles of hydroxyapatite with an average particle size in length (l), width(d) and thickness(h) of about $l = 0,06 \mu\text{m} \pm 50 \%$, $d = 0,015 \mu\text{m} \pm 50 \%$ and $h = 0,005 \mu\text{m} \pm 50 \%$.

3. The stomatic composition according to claim 1 characterised in that it comprises particles of hydroxyapatite with an average particle size in length (l), width(d) and thickness(h) of about $l = 0,06 \mu\text{m}$, $d = 0,015 \mu\text{m}$, $h = 0,005 \mu\text{m}$.

4. A stomatic composition characterised in that it comprises particles of hydroxyapatite having a specific surface of hydroxiapatite from about 100 m^2/g to about 150 m^2/g .

5. The stomatic composition according to one of claims 1 to 4 characterized in that it comprises said hydroxyapatite particles ultra finely divided.

6. The composition according to one of claims 1 to 5 characterised in that the ultra finely divided hydroxyapatite particles are present in the composition in an amount of 0,1% to 50% by weight.

7. The composition according to one of claims 1 to 6 characterised in that the ultra finely, divided hydroxyapatite is a synthetic hydroxyapatite which contains 99,9% of $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ by weight.

8. The composition according to one of claims 1 to 7 further characterised by at least one substance of the group consisting of

- humectants in a range from about 0% to 85% by weight,
- bindings and thickeners a range of 0% to 10% by weight,
- abrasive materials in a range from 0.0% to 25%,
- Surfactants in a range from 0% to 5% by weight,
- Flavours in a range from 0% to 5% by weight.

9. The composition according to one of claims 1 to 8 further characterised by agents enhancing the gingivitis system of the mouth cavity and comprising extracts of natural plants including at least one of the group consisting of urtica, millefolium, chamomilla hypericum, salvia, etc. in the aqueous an in the aqueous-alcoholic form.

10. The composition according to one of claims 1 to 9 further characterised by antimicrobial and anti-plaque agents..